Antenatal AVSD diagnosis at Groote Schuur Hospital

A retrospective cohort study.

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DECLARATION

I, *Dr Charlene Adjoa Adobea Annor*, hereby declare that the work on which this dissertation is based is my original work and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

The antenatal diagnosis of a fetal atrioventricular septal defect (AVSD) impacts the prognosis of an unborn child, and may have psychosocial and financial implications for mothers receiving this diagnosis. Outcomes relevant to our local population may be used to improve counselling for parents receiving this diagnosis. During a literature review, there was a lack of existing published data on antenatal AVSD outcomes from the developing world.

To ascertain the outcomes of antenatal AVSD diagnosis in fetal, neonatal and infant life, we performed a retrospective study of all AVSD's diagnosed at a tertiary referral hospital in Cape Town (Groote Schuur Hospital) between 1 January 2010 and 31 December 2016. We examined ultrasound records and case folders from the antenatal, neonatal and infancy periods, up to a year of life or demise. The resultant cohort had a total of 55 cases.

We found that fetal outcomes in Cape Town, South Africa are similar to those in developed countries. Pregnancies were terminated in just over a third of cases and similarly, the over-all survival to one year of life excluding termination of pregnancy was 29,73%. The bulk of these fetuses demised in the antenatal period, and the rate of demise positively correlated with the presence of associated organ abnormalities and aneuploidies. In those born alive, the correlation between an antenatal AVSD diagnosis and the same diagnosis during postnatal echocardiography was 59,09%, with the remaining 40,91% having other complex cardiac abnormalities diagnosed. Corrective cardiac surgery in the neonatal period or infancy occurred in 46,15% of those born alive, with good outcomes.

This study shows similarity between survival of fetuses diagnosed with antenatal AVSD in the developing and developed world. It will be instrumental in appropriately counselling South African parents who receive the diagnosis. In order to assess if prenatal AVSD diagnosis improves neonatal and infant outcomes, a further study comparing this group to the outcomes of infants with postnatally diagnosed AVSD is necessary. More research is needed in an African context regarding the outcomes of babies diagnosed with antenatal anomalies.

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ABBREVIATIONS

ASD	atrial septal defect
AV	atrioventricular
AVCD	atrioventricular canal defect
AVVR	atrioventricular valve regurgitation
AVSD	atrioventricular septal defect
cAVSD	complete atrioventricular septal defect
CNS	Central nervous system
ECD	Endocardial cushion defect
GIT	Gastro-intestinal tract
GUT	Genito-urinary tract
GSH	Groote Schuur Hospital
ISNPCHD	The International Society for Nomenclature of Paediatric and Congenital Heart Disease
IUFD	Intra-uterine fetal demise
MSK	Musculoskeletal system
RCCH	Red Cross Children's Hospital
t13	Trisomy 13
t18	Trisomy 18
t21	Trisomy 21
TOP	Termination of pregnancy
VSD	Ventricular septal defect

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

The diagnosis of a fetal congenital abnormality affects the projected life expectancy and quality of life of an unborn child, and may have psychosocial and financial implications for mothers receiving this diagnosis. Babies born with congenital abnormalities may require prolonged neonatal admission, surgery, speech therapy and occupational therapy, simply to survive. The effect of this burden may be compounded in a resource-limited setting where health services available to babies born with congenital abnormalities may not be optimal. Knowledge of the prognosis and management options for the specific defect in our own context is therefore important.

The aetiology of congenital cardiac defects is usually unclear; especially in non-syndromic congenital heart disease. These non-syndromic cases constitute about 85% of cases. In the remainder, aneuploidies such as Down's syndrome, DiGeorge syndrome, Turner syndrome, Edward syndrome and Patau syndrome, are associated with 8 to 10% of all congenital cardiac defects. In 3-5% of cases, single gene defects may be associated. Various risk factors have been shown to be associated with congenital cardiac defects. These include maternal diabetes, smoking, maternal obesity, alcohol use, rubella infection, pre-eclampsia and phenylketonuria. [1] [2]

Though there are a vast number of congenital cardiac defects, atrioventricular septal defects (AVSDs) constitute 3-5% of the group. In 2006, the incidence was recorded as 1 in 2 120 in the United States. AVSDs contribute substantially to the morbidity and mortality impact of congenital heart disease. Depending on the size and location of the defect, affected individuals may be symptomatic from as early as 6 weeks of life, while others may present in the second or third decade due to pulmonary complications.

Once an AVSD is identified, medical treatment may improve quality of life, improve the ability to thrive and reduce the rate of complications. Corrective surgical measures are available in our setting, and can be performed when indicated. Infants in whom the diagnosis is missed may present late, as they may be asymptomatic at birth. Complications, such as pulmonary hypertension, are irreversible once severe.

Antenatal diagnosis therefore forms an important part of the management of all congenital cardiac defects by reducing the number of infants that are missed in the neonatal period. In addition, associated abnormalities are identified sonographically and a prenatal genetic diagnosis can be made. [3]

BACKGROUND: CONGENITAL CARDIAC DEFECTS IN AFRICA

Fetal congenital cardiac defects occur in 8 per 1000 live births. The true incidence is estimated to exceed this, as congenital anomalies occur more frequently in the still birth and preterm birth populations. In recent years, early antenatal diagnosis, neonatal medical management and surgical correction of congenital cardiac defects has dramatically reduced the mortality rate amongst affected infants. There has been a 39% reduction in the mortality rate overall in U.S. trends over the period 1979-2014. [2] [1]

Despite these advances, the age adjusted death rate for patients with congenital cardiac defects is still higher than in the unaffected population. In the United States the infant mortality rate for congenital heart disease as well as the post-surgery mortality rate seems to be statistically worse in minority groups (Black and Hispanic) when compared to the white majority group [39,6 and 32,2 vs 30,1%]. It is unclear whether this difference is related to socioeconomic disparities or a difference in the care obtained. [2]

While these figures from the U.S. are helpful, they don't give us an accurate idea of what is happening locally. There is a lack of data from South Africa and Africa

detailing the prevalence of congenital heart disease. A cross-sectional study performed in 2006 in Mozambique detected a congenital heart disease prevalence of 2,3 in 1000 amongst public school going children; 80% of these were new diagnoses. The prevalence rate calculated in this study did not account for those born with severe disease who may have demised before school going age. [4]

In older African studies, the following prevalence rates were found: 3,5 per 1000 live births (found in 4220 consecutive births in Nigeria in the 1960s) and 3,9 per 1000 school children (found in school children in Soweto, Johannesburg in the 1970s). [5, 6]

The few available African statistics may be gross underestimates for a number of reasons:

- The level of access to antenatal sonography screening is poor in Africa.
- Access to a routine medical neonatal examination is not guaranteed, so cardiac defects in neonates are more often than not missed in the neonatal period.
- As a result, many diagnoses are made in late childhood or early teen years, when irreversible lung pathology often precludes surgical repair.
- There are a number of undiagnosed cases that result in early "unexplained" neonatal, infant or childhood deaths and are not counted in prevalence statistics.

Even if diagnosed timeously, resultant neonatal morbidity and mortality is higher in Africa as access to paediatric services is poor, there are a limited number of trained paediatric cardiologists on the continent, and there are fewer centres that offer these specific surgical services. These centres are inundated with long waiting lists, with many patients dying whilst awaiting surgery. [7] [8]

While developed countries have seen a huge improvement and a "changing face" of congenital heart disease over the past 50 years, Africa has not enjoyed the same benefit. Congenital heart disease in Africa is underestimated, undiagnosed and there

is a paucity of data on the subject. We need further research in the area to establish actual prevalence and the burden of the disease.

BACKGROUND: ATRIOVENTRICULAR SEPTAL DEFECTS

AVSDs or atrioventricular canal defects (AVCDs) are fetal cardiac congenital abnormalities caused by the failure of fusion of endocardial cushions during embryogenesis. The defect can be diagnosed antenatally with reasonable accuracy, and constitutes 4-7% of all infants with congenital heart disease. The frequency of this anomaly is 0,19-0,53 per 1000 live births. This frequency increases in association with Down syndrome and other chromosomal abnormalities. [9] [10]

AVSD and AVCD are synonymous with endocardial cushion defects. They will be referred to by the former in this study.

Anatomically, they are a spectrum of lesions involving the endocardial septum at the level of the common atrioventricular junction. There are varying degrees of hypoplasia of the septal tissue adjacent to the atrioventricular (AV) valves, with associated varying degrees of valvular hypoplasia. The size and location of the defect influences the degree of functional impairment and therefore the prognosis. The spectrum of disease includes defects in the inferior (or posterior) portion of the atrial septum, defects in the inflow portion of the ventricular septum and defects in the tissue forming the right and left AV valves. [9]

Various classification systems exist to type the defects according to anatomical location, functional impairment or prognosis. These are, however, postnatal classification systems. The International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD) classifies AVSD as follows:

- Complete AVSD: comprises an ostium primum (ASD) with a non-restrictive defect in the inlet portion of the ventricular septum.
- Partial AVSD: these include

    - Isolated Atrial Septal Defect (ASD) – also known as ASD primum, ostium primum defect. Here the valvular leaflets are attached to the ventricular septum.
    - Isolated ventricular septal defect (VSD) - also known as an inlet VSD. Here the partially fused valve leaflets are attached to the atrial septum
- Intermediate AVSD: an ostium primum ASD with a VSD just below; this is often restrictive. Here there are two separate AV orifices with fused leaflets centrally. [10]

Another postnatal classification system for complete AVSDs specifically is the Rastelli classification. It was initially formed to predict operative outcomes, but currently, it is infrequently used as there are few retrospective correlation studies to actual clinical outcomes. Rastelli classification type C, which shows bridging of the VSD by a single, unattached bridging leaflet, typically has the worst prognosis, even after surgery. [10] [11] [12]

AVSDs can also be classified as "unbalanced" if they have an associated degree of ventricular hypoplasia or a malalignment of the intraventricular septum caused by a difference in ventricular sizes. An unbalanced AVSD occurs in heterotaxy syndrome, mentioned below. [10] [11] [12]

Antenatally, the presence of a normal "crux" at the centre of the heart is an informal way of classifying AVSDs. The "crux" visualized sonographically is the insertion point of the right and left atrioventricular valves onto the septum, and is clear with off-setting in a normal heart. The absence of a "crux" (hole at the centre of the heart), would correlate with a Rastelli C type AVSD, and is the easiest to see. A linear insertion of AV valves (no off-setting) would correlate with a Rastelli type B. The hardest to see, would be those with the presence of normal off-setting at the "crux", but an unstable or kicking crux – this would correlate with a Rastelli A type. [13]

It is well appreciated that the spectrum of antenatal disease differs from the postnatal one. There are more severe forms of the disease and a greater frequency of

associated anomalies in the antenatal population, as these commonly result in fetal or neonatal deaths. Various studies have reported on the attrition rate of these fetuses, and the rate is influenced by the rate of choice of termination of pregnancy. A Birmingham study published in 2008 had a rate of 46,7% perinatal deaths if termination of pregnancy and loss to follow up were excluded. In a 2009 Turkish study, a perinatal death rate of 34,6% was found, with a higher termination of pregnancy rate. [14] [15] [16]

PATHOGENESIS

The pathophysiological mechanism of an AVSD can be noted from the 9th week of gestation, and can be detected from the 12th gestational week. [10]

At 3 weeks gestation, the primary heart tube forms from the splanchnic mesoderm. Two areas develop in this tube: the myocardial progenitor population and the second heart field population. The second heart field population of cells are progenitors for the outflow tracts. From the myocardial progenitor population, two separate layers delineate: an external layer which develops into myocardium, and an inner layer (endothelium) which forms the endocardium. The two layers have gelatinous connective tissue between them called cardiac jelly. In the fourth gestational week this initial common atrioventricular tube is then divided into two by the development of the endocardial cushions, which develop in the dorsal and ventral surfaces of the tube from the cardiac jelly. Mesenchymal cells invade these cushions; they then grow towards each other and fuse centrally separating the primordial atrium from the ventricle. [17] [3]

A curtain- like growth then starts from the roof of the primordial atrium and grows towards the endocardial cushions; this is called the septum primum. This divides the atrium into right and left, initially leaving a gap called the foramen primum just above the fused endocardial cushions, which later closes. Perforations higher up in this membrane form and later coalesce to form the foramen secundum. The atrial

part of the AV septum is reinforced by the septum secundum which is more muscular and grows from the myocardial wall. The oval foramen lies in the septum secundum and partially overlies the foramen secundum. Because of this second layer the mature foramen secundum then functions as a shunt with a valve-like mechanism ready to close it after birth. [17] [3]

Ventricular septal development occurs as ridges of myocardium grow upwards from the apex of the ventricular floor. These ridges come from both the right and left ventricles and are called the right and left bulbar ridges. This divides the ventricles into left and right but leaves a gap, an intraventricular foramen (between the bottom edge of the fused endocardial cushions and the top of the intraventricular (IV) septum), that persists up until the 7th week. [17] [3]

Finally, closure of this intraventricular septum occurs. A membrane grows from the right side of the endocardial cushion to the muscular IV septum. It is through failure of this final step, or any step involving endocardial cushion development that an AVSD can form. [17] [3]

ULTRASOUND AND ANTENATAL DIAGNOSIS

Access to antenatal screening sonography is improving in South Africa. Antenatal fetal anomaly diagnosis may improve the outcome of affected fetuses by identifying them as high risk, and setting in motion a pre-natal and postnatal management plan. It also gives mothers the right to choose to continue a pregnancy when a fetus is known with a significant or lethal anomaly.

Sonographic detection rates of fetal anomalies are affected not only by the experience of the practitioner, but the transducer and ultrasound equipment, the patient's degree of central adiposity, any abdominal scars that may overlie the area being scanned, gestational age, amniotic fluid volume and fetal position. [18]

A mid-gestation (20-22 weeks) detailed anatomical screening scan is recommended for all pregnant women. Prior to this, pregnant women at high risk for fetal anomalies (advanced maternal age, maternal diabetes and previous children with heritable anomalies) are offered nuchal translucency screening at 12-14 weeks. Cardiac anomalies can be identified earlier than the mid-gestation scan, especially when pregnancies have been flagged by the presence of nuchal oedema at 12-13 weeks. [18] [19]

AVSDs are optimally diagnosed on an apical 4 chamber view of the heart; as early as 12 weeks gestational age. They are identified optimally during diastole, during which time a large central defect in the centre of the heart can be seen, affecting the atrial septum, ventricular septum and the atrioventricular valves. The valve may sometimes appear as one single valve stretching across the heart during systole, with no attachment to the ventricular or atrial septum. [9] [10]

In the four-chamber view, the leaflet of the tricuspid valve attached to the septum normally inserts lower down (closer to the apex) than the corresponding insertion of the mitral valve. This is called an "off-set" of the valves. Lack of an offset would be identified as a common or linear insertion and give the appearance of one single valve stretched across the heart. Other features used to identify an AVSD prenatally include: a large discontinuity in the cushion zone of the AV septum, atrial and ventricular defects of varying sizes, an aorta unsprung from the crux of the heart and an unstable/floating/kicking crux. [16]

In addition, examining the heart in the outflow tract and 3 vessel view is important in order to identify common associated cardiac abnormalities: for example atrial isomerism in heterotaxy syndrome and pulmonary stenosis in tetralogy of Fallot. Two-dimensional (B-mode), colour and Doppler flow mode as well M-mode (for arrhythmias) are used to assess the fetal heart. The presence and degree of atrioventricular valve regurgitation is also assessed and graded antenatally with Doppler studies.

The diagnosis of AVSD is often missed if antenatal sonographic screening is not performed at a centre dedicated to fetal anomaly screening. The detection rate has been shown to be as low as 29%, which improves to 67% for balanced AVSD and 93% for unbalanced AVSD with adequately trained sonographers. [20] [21]

Beyond this, detailed antenatal sonography is needed to identify associated abnormalities in various organ systems, which may affect the prognosis of a fetus with an AVSD.

FACTORS AFFECTING PROGNOSIS

There are various factors which affect the prognosis of an AVSD. These include associated structural abnormalities (cardiac and non-cardiac), associated chromosomal abnormalities, ventricular size, heterotaxy and valvular regurgitation.

Associated structural abnormalities may be cardiac or non-cardiac in origin and they play a role in the prognosis of an AVSD diagnosis. Common associated abnormalities include:

1. Heterotaxy syndrome (occurs in up to 45%) is also known as situs ambiguous and isomerism. In heterotaxy syndrome, organs in the chest or abdomen have a partial defect of left-right laterality. Unlike situs inversus, organ systems are incompletely reversed, and the partial disorientation causes major abnormalities in cardiac and blood vessel development. These defects cause significant and even fatal disruptions in the function of organs. The cardiac defect in Heterotaxy Syndrome commonly involves an AVSD in association with either atrial isomerism (two left atria or two right atria), Ebstein's anomaly or transposition of the great arteries. Other organ anomalies in Heterotaxy syndrome include: bronchial and biliary tree abnormalities, malrotation, and polysplenia. A fetus diagnosed with an AVSD in association with heterotaxy syndrome therefore has a worse prognosis. They may need

corrective surgery not only for the AVSD, but also for additional anomalies (e.g. The Kasai procedure for biliary atresia). [22, 10, 3]

2. Cardiac abnormalities that occur in association with an AVSD include Tetralogy of Fallot, sub-aortic stenosis, an anterior aorta, ventricular hypoplasia, short ventricular septum, coarctation of the aorta and double outlet right ventricle. Associated cardiac abnormalities are often present fetuses with a normal karyotype (non-syndromic). Various studies show that an AVSD will have an associated cardiac anomaly in 48 to 58% of cases. [10] [16]

3. Other organ system abnormalities – Up to 75% of fetuses diagnosed with an AVSD will have associated defects in other organ systems.

Chromosomal abnormalities occur in 26-58% of AVSDs. AVSDs with associated chromosomal abnormalities are called syndromic AVSDs. Most are commonly associated with Down syndrome. For this reason, it is important to offer a diagnostic amniocentesis in all patients with AVSDs. Other genetic associations include trisomy 18, trisomy 13 and triploidy. Syndromic AVSDs do not usually have associated cardiac abnormalities. [10] [14] [23]

Ventricular size: Due to haemodynamic changes during fetal life, the nature of a defect and therefore the prognosis may change during the antenatal period. This physiological change occurs because there is a reduction in after-load (as placental resistance reduces) and an increase in pre-load as gestation advances (due to fetal blood volume increasing). The presence of an AVSD can result in ventricular re-modelling. This results in unbalanced ventricles where hypoplasia of one of the ventricular chambers is noted on ultrasound. Unbalanced AVSDs are associated with poorer surgical outcomes and are offered palliation when severe. [24] [12]

Associated valvular hypoplasia affects the prognosis of a fetus with an AVSD. Abnormal valves result in atrioventricular valve regurgitation (AVVR) (mitral

regurgitation, tricuspid regurgitation, or both). During fetal life, the degree of regurgitation can worsen, improve, or stay the same – and the prognosis changes along with it. AVVR is graded antenatally as mild, moderate, and severe. Surgery may or may not correct regurgitation, and uncorrected significant regurgitation may be symptomatic in the long term and present as congestive cardiac failure in an infant. [24]

The antenatal diagnosis of these associated features is important as they may impact on prognosis. Noting the presence of these features is important when counselling parents.

PROGNOSIS AND MANAGEMENT: FETAL AND PERINATAL OUTCOMES

The natural history of AVSDs differs according to the position, the extent of the lesion, any associated valvulopathy and any associated cardiac abnormalities. Shunting occurs through the defect from the left to the right side of the heart, as long as there is no associated right ventricular outflow obstruction. The resultant increase in right sided heart pressures, causes progressively increased pulmonary vascular congestion.

In *complete* AVSDs, survival without surgery is poor. Premature death may occur in infancy due to congestive cardiac failure or pneumonia. [11] [16, 25, 16] Infants develop a failure to thrive. If they survive infancy, the development of irreversible pulmonary vascular obstructive disease limits childhood survival. This begins at 6-12 months, and is more rapid in infants with Down syndrome. Surgery is therefore recommended in infancy, and has an estimated mortality rate of 3,6% and a re-operation rate (later in life) of 11% in the USA. [26]

With *partial and intermediate* AVSDs, the shunt throughout the atrial component of the AVSD is well tolerated throughout the first decade of life. Patients may be asymptomatic until adolescence, when they may report exercise intolerance. The presence of associated moderate or severe mitral regurgitation may still cause congestive cardiac failure or failure to thrive and necessitate earlier surgical correction. [27]

It is important to note that the outcomes and spectrum of antenatally diagnosed AVSD and postnatal AVSD diagnosis differ greatly. Studies regarding children with a postnatal diagnosis commonly show a survival rate on >80%, whereas in antenatally diagnosed AVSD case series' the survival rate rarely exceeds 45 - 60%. In the antenatally diagnosed group, the spectrum is wider and severity varies greatly. The group that survives the fetal and peri-natal period has better outcomes. [28] [9]

IMPACT OF CARDIAC DISEASE ON FAMILIES: COSTS AND PSYCHOLOGICAL STRAIN

Having a healthy child is ideal. Unfortunately, for some parents, the diagnosis of a fetal congenital abnormality affects the projected life expectancy and quality of life of their unborn child. Financial and psychological strain affect the entire family.

Parents need psychological support and counselling. Antenatal counselling detailing the expected prognosis based on similar infants diagnosed with AVSDs in our local setting is important. Once adequate counselling has been given, parents are more readily prepared to make an informed decision if medical TOP and amniocentesis are offered.

For parents who choose to continue the pregnancy, knowledge of the potential expected interventions and survival rates in the perinatal period and in infancy is helpful.

GLOBAL OUTCOMES

There are a few studies looking at fetal and perinatal outcomes of antenatal AVSD diagnosis. These, however, are from the developed world.

A retrospective review in Minnesota (USA) involving 31 cases of cAVSD diagnosed between 18 and 29 weeks gestational age was performed. The cases were analysed for gestational age, the diagnosis of chromosomal abnormalities, echocardiographic findings postnatally and the fetal and neonatal course. Their findings included the following:

- 50% of the cases had associated chromosomal abnormalities
- 33% had heterotaxy syndrome
- 10% opted for termination of pregnancy
- 22% had spontaneous closure of the VSD component in utero.

- For those cases that had an operative intervention planned, 3 out of 18 demised prior to surgery, 15 underwent repair and 1 demised due to an intra-operative complication (shunt thrombosis) [9]

In a similar study in Turkey (published 2008), following outcomes of 62 antenatally diagnosed AVSDs from 2002 to 2007:
Associations:

- 19% were associated with heterotaxy syndrome
- 63% had extra-cardiac anomalies
- 55% had associated cardiac abnormalities
- 33% had chromosomal abnormalities (almost half of which were Trisomy 21)
- 58% chose termination of pregnancy
- 6,4% had intrauterine fetal deaths
- 8% resulted in neonatal deaths without surgery (amounted to 22,7% of live births)
- 27% underwent surgery (77% of live births)
- 20% were alive at the date of publication (2-5 years old), amounted to 59% of live birth. [16]

Again, there were no published studies conducted in an African or developing world context identified.

CONCLUSION

AVSDs constitute 5-8% of cardiac congenital abnormalities diagnosed antenatally. [27] They can be diagnosed as early as 12 weeks, and can be associated with genetic abnormalities (especially trisomy 21) as well as other congenital abnormalities (heterotaxy syndrome, systemic anomalies and other cardiac defects).

The severity of the defect depends on whether it is complete or incomplete, has any associated valvulopathy or the presence of any additional cardiac abnormality. Prognosis is further affected by the presence of other extra-cardiac fetal anomalies or chromosomal abnormalities.

Antenatal ultrasound can be used to diagnose the AVSD, along with associated cardiac and non-cardiac abnormalities. Parents can then be counselled about the prognosis based on these sonographic findings. Termination of pregnancy may be offered in some cases. Surgery may be offered in infancy if the defect is complete, or is associated with moderate to severe mitral regurgitation

There have been previously published studies on the outcomes of atrioventricular septal defects following antenatal diagnosis. These studies were conducted in the developed world. There is a lack of published outcomes from the African continent.

CHAPTER 2: PUBLICATION READY MANUSCRIPT

Introduction

Atrioventricular septal defects (AVSDs) constitute 5-8% of congenital cardiac abnormalities. [27] In 2006, the incidence was recorded as 1 in 2 120 in the United States. AVSDs contribute substantially to the morbidity, mortality and impact of congenital heart disease worldwide. There is a paucity of data pertaining to prevalence and outcomes from South Africa and Africa. [2] Knowledge of South African and African outcomes is essential if we are to appropriately counsel parents who have received a diagnosis of fetal AVSD.

The aim of this study was to assess the outcomes of fetuses diagnosed with an AVSD at the Fetal Medicine assessment clinic at Groote Schuur Hospital (GSH) over a 7 year period in the form of a retrospective cohort study. Outcomes were assessed from the time of antenatal diagnosis until the point of demise (fetal, neonatal or infant death) or up until a year of life.

Background

An AVSD is caused by an inadequate endocardial cushion and cardiac septal development. The lesion can be diagnosed as early as 12 weeks' gestation on an antenatal ultrasound, but is commonly diagnosed after 20 weeks. [10]

This congenital defect can be associated with genetic and/or other structural abnormalities. AVSDs that occur with a normal genotype are termed non-syndromic AVSDs and occur 37-58% of the time. In a recent study in Minnesota, 50% of their AVSD cases had an associated genetic abnormality. In another study performed in Turkey in 2008, 33% of their cases had an associated genetic abnormality. Associated genetic abnormalities include trisomy 21 (this is the most common), trisomy 18, trisomy 13 and triploidy. [9] [16]

The severity of the defect depends on whether it is complete or incomplete, the degree of atrioventricular valve regurgitation that develops and if there is any additional cardiac anomaly. This wide spectrum affects prognosis. Prognosis is further affected by other fetal anomalies in other organ systems.

Antenatal ultrasound can be used to diagnose the AVSD, along with associated cardiac and non-cardiac abnormalities. Based on sonographic screening, patients are offered invasive testing to identify possible genetic abnormalities. Parents are then counselled about the prognosis based on these sonographic findings. Termination of pregnancy may be offered in some cases.

Antenatal diagnosis enables us to plan with neonatologists as well as paediatric cardiologists to optimise the outcomes for these children. Surgery is offered in infancy (around 3 months) if the defect is complete, or is associated with moderate to severe mitral regurgitation, in order to prevent the development of pulmonary hypertension. [10]

Obtaining an indication of survival rates in our local setting allows us to appropriately counsel women diagnosed with this fetal anomaly in South Africa.

Methods

The study is a retrospective cohort study. Groote Schuur Hospital (GSH) is a tertiary hospital that services the entire Cape Town Metro West district. All patients with abnormal fetal sonography performed at primary and secondary level in the district are referred for review at the GSH antenatal sonography department. In this study, the AVSDs picked up antenatally were discussed and a multidisciplinary plan made between obstetricians, neonatologist and at times; paediatric cardiologists at GSH.

Inclusion Criteria

All mothers diagnosed with AVSDs within a seven-year period (between 1 January 2010 and 31 December 2016) at the Fetal Medicine Unit at GSH were identified. .

Exclusion Criteria

- All cases of AVSDs that were not diagnosed at our Fetal Medicine Unit. Cases only diagnosed postnatally at our hospital were excluded. As GSH services the district, referral pathways would ensure all antenatally diagnosed AVSDs would be referred to our unit once identified.
- An initial diagnosis of an AVSD that was changed *antenatally* after review with the fetal medicine team or with antenatal review with the paediatric cardiologists.

Retrospective data from antenatal ultrasounds is available on the Astraia® system in the ultrasound department. This is a database that tracks all obstetric and gynaecology ultrasound data in our department since 2010. Patients are informed that their data will be entered into this database prior to their ultrasound. Ultrasound data included: date of diagnosis, gestational age at diagnosis, descriptors of AVSD lesions, associated abnormalities, details of invasive test and TOP counselling and the diagnosis of some fetal antenatal complications.

Data was also obtained from the maternity case records at Groote Schuur Hospital. This included: the demographics of the mother, chronic diseases, results of invasive genetic tests, obstetric complications, TOP or delivery details and fetal post mortem findings (if performed).

Linked paediatric files (at both GSH and Red Cross Children's Hospital {RCCH}) were sourced for additional outcome data. The neonatal and infant outcomes were followed up until demise or a year of life. Other neonatal and paediatric details included surgical procedures performed, number of days in ICU, duration of general admission in the neonatal period and infancy, results of genotype and post-mortem results (if performed).

Our primary outcome of the study was to approximate the fetal, perinatal and infant survival outcomes of babies diagnosed with AVSDs antenatally in the past 7 years at

Groote Schuur Hospital. Additionally, we wanted to assess the impact of genetic abnormalities and/or additional structural abnormalities on the survival rate.

Secondary outcomes were to assess the characteristics of the cohort, for example:

- The identification of the rate at which mothers choose medical termination of pregnancy after receiving this antenatal diagnosis. The associated prognostic factors which may contribute to this decision will be highlighted.
- To identify maternal risk factors e.g. age, presence of diabetes, smoking, teratogens or a previous fetus affected with an anomaly.
- Frequency of acceptance of amniocentesis, and the prevalence of genetic abnormalities in the cohort.
- Associated fetal abnormalities and their frequency.
- The survival impact of having an AVSD with a chromosomal abnormality vs an AVSD with a normal genotype.
- The survival impact of having an AVSD with other associated congenital abnormalities vs an isolated AVSD.
- Assessment of the accuracy of our antenatal diagnosis of AVSD as compared to postnatal diagnosis
- Rates of miscarriage, intra-uterine fetal demise (IUFD), neonatal and infant mortality rates for this cohort with AVSD.
- Morbidity during the first year of life can be gauged: using duration of hospital stay and the number of surgical procedures the infant was subjected to.
- Survival rates following surgery for AVSD

Missing Data

Mothers who were subsequently lost to follow up, had missing folders, or whose neonatal/infant folder could not be identified were included in the study. Their case data was included as far as documented.

Sample Size

As this was a retrospective cohort study, the limiting factor was the time period over which the study was being conducted. Our initial rough estimate of the number of mother-child pairs to be identified was 70 pairs.

Data Handling

Data was reported in data collection sheets, attached in the appendix. Linked mother-neonatal and neonatal-paediatric pairs were given a confidential unique study number. Only the principal investigator had access to a document correlating study numbers to hospital numbers in the two different hospitals. This data was then transcribed into tables on Microsoft Excel.

Data Analysis

University of Cape Town Statistical Consulting Services assisted with data analysis and interpretation. Descriptive statistics were used to detail the cohort, associations were mostly analysed with the Fishers exact, two sample T-test and the Chi-squared test where indicated. Kaplan Meier survival estimates were utilised to graphically display survival curves for the cohort.

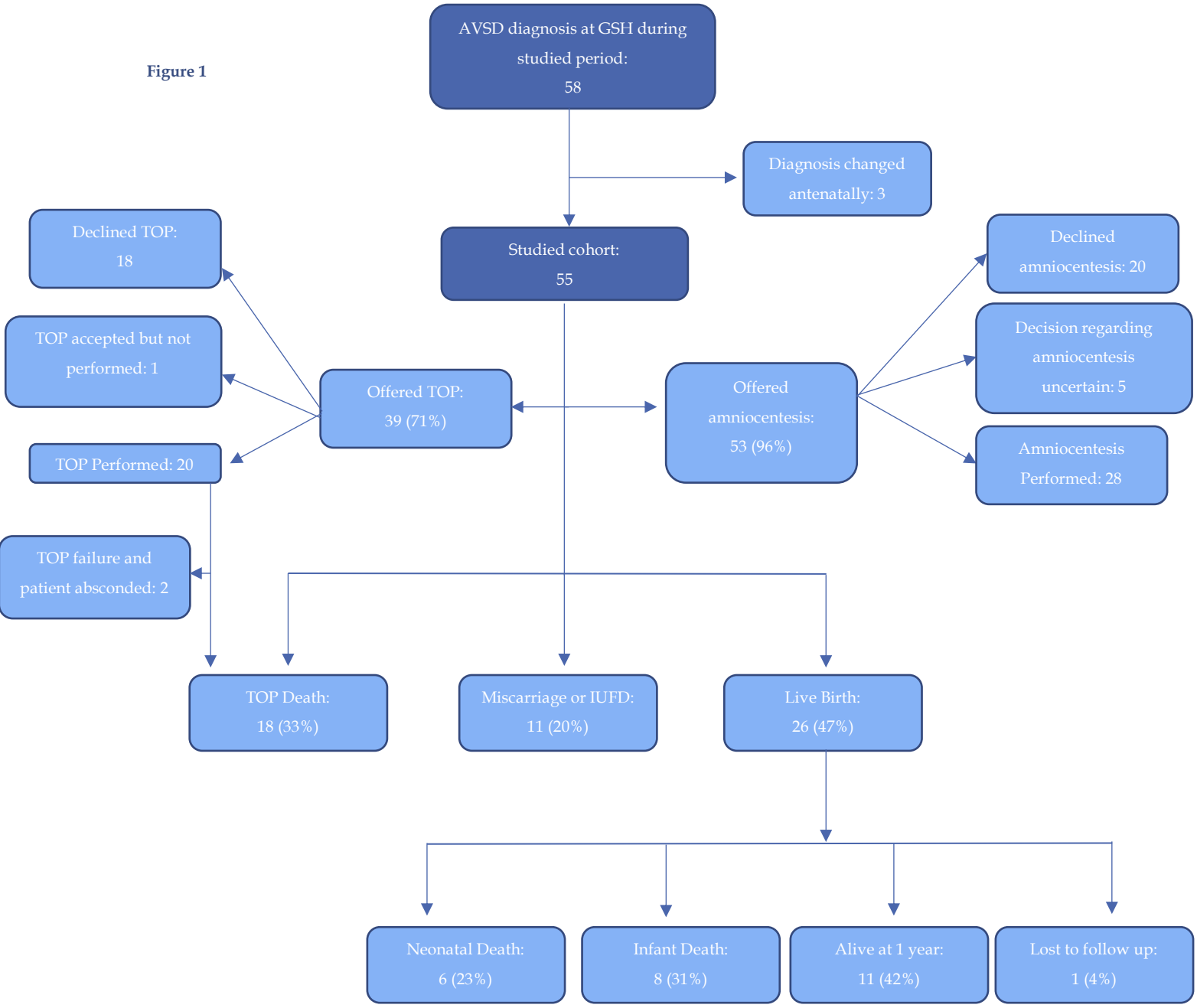
Results

There were 58 cases of AVSD diagnosed in the study period at Groote Schuur Hospital. Three (n=3) of these cases were excluded as their antenatal diagnosis was changed to hypoplastic left heart syndrome, Tetralogy of Fallot and a ventricular septal defect (only) respectively. The residual cohort was 55.

The average age of the mothers with an AVSD diagnosis in the study was 31,6 ± 7,5 years. They had an average BMI of 27,3 ± 6,4 and smokers constituted 14,4% of the group. The most common referral reason was an abnormality found at secondary level anomaly scan (63,6%); and the average gestational age at diagnosis with us was 23 weeks.

Twelve mothers (n=12, 21,8%) had either chronic or gestational diabetes. Only 2 mothers (n=2, 3,6%) had had a diagnosis of a fetal anomaly in a previous pregnancy. In two patients, family members with a congenital musculoskeletal defect were identified and a 2nd degree relative with a congenital cardiac anomaly. Periconceptional use of Roaccutane was identified in 2 cases, other possible teratogens identified included: methamphetamines (n=1), enalapril (n=1) and an unspecified anti-epileptic (n=1).

Figure 1



The vast majority of the group was described as having a "complete" AVSD (n=50, 90,9%). Descriptors of AVSD:

- Off-setting of the valves was only commented on 20% of the time (n=11). When mentioned, a lack of normal off-setting of valves was described in 91% (10 out of 11 cases).
- Ventricular hypoplasia, or the presence of balanced or unbalanced ventricles was commented on 52,7% of the time. In those commented on, 68,9% had unbalanced ventricles i.e. the presence of ventricular hypoplasia.

Associated structural anomalies:

An isolated AVSD was identified in 32,73% (n=18). Sixty-seven percent (67,27%, n=37) of our group therefore had an AVSD with another associated fetal abnormality. The average age of those with an additional fetal abnormality compared to those without was 34,6 ± 6,05 years vs 30,2 ± 7,8 years. Figure 1 shows the frequency of associated abnormalities in different organ systems. Most of these cases had more than one associated abnormality.

Figure 2

Associated Anomaly	Frequency	Frequency Percentage
None (Isolated AVSD)	18	32,73%
Additional cardiac (± in addition to other anomalies)	19	34,55%
Additional non-cardiac abnormality (total group)	30	54,55%
Musculoskeletal	15	27,27%
Central nervous system	11	20,00%
GIT	8	14,55%
Heterotaxy Syndrome	7	12,73%
Genitourinary	5	9,09%
Pulmonary	2	3,64%
***some cases had more than one additional anomaly, this table is not summative**		

- An associated cardiac abnormality was the most common associated abnormality: in over half of the cases that had an additional anomaly, an additional cardiac anomaly was present (51,3%). Associated cardiac abnormalities included: an overriding aorta, aortic stenosis, interrupted aortic arch, pulmonary valve atresia, double outlet right ventricle, transposition of the great vessels, common atrium, endocardial fibro-elastosis and an echogenic tumour of the left ventricle.

- Musculoskeletal (MSK) anomalies included: bilateral cleft lip and palate, skeletal dysplasia, short ribs, sacral agenesis (part of Ivemark Syndrome), micrognathia, abnormal hands, cystic hygroma, midline facial cleft and talipes equinovarus.

- Associated central nervous system (CNS) anomalies included: vermian hypoplasia or Dandy-Walker syndrome, ventriculomegaly, dilated cisterna magna, small cerebellum, alobar holoprosencephaly, occipital encephalocoele and agenesis of the corpus collosum.

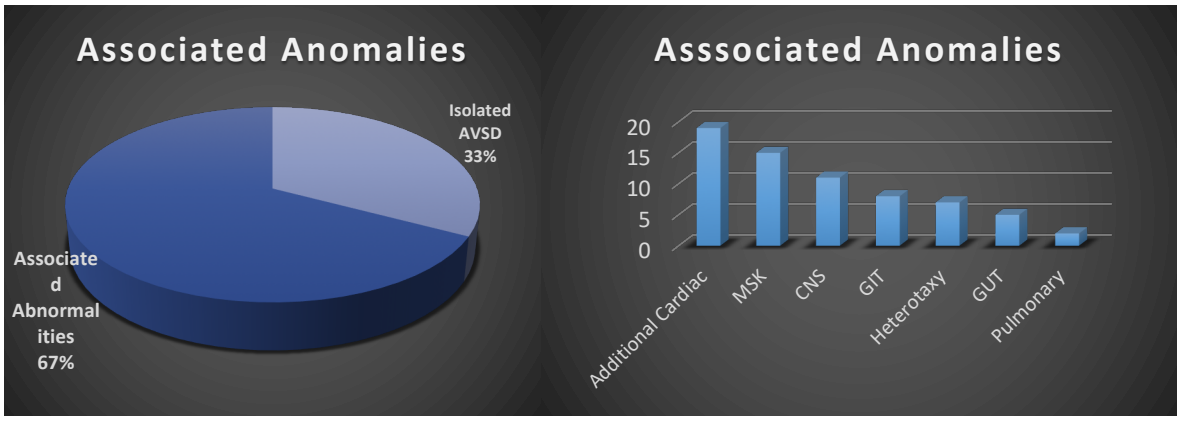
- Associated gastrointestinal system (GIT) abnormalities included: duodenal atresia, oesophageal atresia, omphalocoele and a cystic stomach mass.

- The frequency of heterotaxy syndrome was 12,73%. This was identified in the following ways: polysplenia, asplenia, situs inversus abdominus and right or left atrial isomerism.

- Associated genitourinary (GUT) anomalies included: hydronephrosis, dilated pelviureteric junction and a solitary kidney.

- Uncommonly, respiratory system anomalies were found in association with our AVSDs (only 2 cases). The anomaly noted was pulmonary hypoplasia in both of these cases.

Figure 3



Amongst the diabetic group (n=12): 4 had heterotaxy syndrome, 4 had additional associated cardiac abnormalities, 3 had associated musculoskeletal abnormalities and 5 had isolated AVSDs (some had a combination of 2 or more additional anomalies).

Associated genetic abnormalities:

The karyotype of affected fetuses was detected on either amniocentesis or postnatal genotyping from peripheral blood.

Amniocentesis was offered in 96,36% of cases. There were 2 cases where amniocentesis was not offered; reasons were advanced gestational age at presentation (37 weeks) and absent or reversed end-diastolic flow at 28 week presentation.

In those who were offered amniocentesis, the acceptance rate of amniocentesis was 52,83% (n=28). The procedure was declined was 37,7% (n=20). In the remaining group (n=5, 9,4%) the decision regarding amniocentesis was unknown. In these cases, patients delivered without an amniocentesis being performed. It is not well documented in these cases if the patient declined or accepted amniocentesis prior to delivery.

The average age of those declining amniocentesis compared to those who accepted the procedure was 29,2 ± 6,3 vs 32,1 ± 8,5.

A further 11 cases had a genetic assessment postnatally, so we know the genotype of 70,9% (n=39) of the group. The incidence of an abnormal genetic result was 46% in those that were tested.

Figure 4

Karyotype Results (Combined Amniocentesis and Postnatal Genotype)		
Result	Frequency	Percentage
Not Done	16	29,09%
Normal	15	27,27%
Trisomy 21	12	21,82%
Trisomy 13	1	1,82%
Trisomy 18	5	9,09%
Other*	3	5,45%
Culture Failure	3	5,45%
***Other included: 4q deletion, 6 supraband, derivative 4.**		

Amongst the diabetic group, 58,33% did not have their karyotype assessed, 27,78% had normal result and 16,67% had a trisomy 21 result.

Uptake of Termination of pregnancy (TOP)

Termination of pregnancy was offered in 70,91% (n=39) of cases. Of those cases, 46,15% (n=18) declined the procedure and 53,85%(n=21) accepted it. Of those who accepted TOP, the procedure was successfully performed in 85,71% (n=18). In the remaining three cases, a termination of pregnancy was not successfully performed. In one case, a woman opted for a TOP but this was not performed as she sustained a IUFD prior to her TOP date. In another two cases, patients left the hospital after

failed TOP attempts (one had a stillbirth at 36 weeks, the other a live birth at term – discussed further below). This resulted in a total TOP death rate of 32,72% (18 cases).

The average age of the mothers accepting TOP was similar compared to those who declined TOP (31,05 years vs 31,78 years respectively). The average gestational age at diagnosis in the group who had a TOP performed was 22,15 ± 2,87 weeks and in those who declined it 21,22 ± 4,91 weeks.

Overall, the frequency of TOP in the group with an isolated AVSD was 27,78% and 40,54% in the group with one or more additional anomaly. TOP uptake was highest in the group of fetuses that had associated pulmonary abnormalities (100%, *p=0,172*), associated GIT abnormalities (85,71%, *p=0,049*), followed by those with associated MSK abnormalities (69,23%, *p=0,122*).

Amongst those who had a normal karyotype, 44,44% had a TOP. Cases with the diagnosis of Down syndrome had a TOP frequency of 37,50%. In Patau syndrome this rate was 100% and in Edwards syndrome 80%. Overall, those with an abnormal karyotype had a TOP frequency of 62,50% (*p= 0,325*).

TOP was successful in all cases but two as mentioned above. In one case, after 4 failed attempts at medical TOP, the patient absconded and only returned at term. She delivered a live, 3280g baby: this baby had surgery in infancy and was alive at 1 year after birth. In the second case, the patient declined further treatment after the TOP had been initiated, and returned at 36 weeks with an IUFD.

Miscarriage and Intra-uterine fetal demise (IUFD)

There were a total of 11 cases of spontaneous miscarriage and IUFD (20,00%). A miscarriage or IUFD occurred in 24,32% of those with one or more associated abnormality; as compared to 11,11% of isolated AVSDs, but this difference was not statistically significant. *(p=0,219).* In those with abnormal available karyotype, 9,52% had a miscarriage or IUFD vs 20,00% of those with a normal karyotype, but again this difference was not statistically significant. *(p=0,337)*

Neonatal Period

Twenty six (26) of the affected fetuses were born alive (47,27% of the cohort).

Neonatal resuscitation was needed in 48,15% of cases. Of those needing resuscitation, 61,54% had one or more additional anomaly (*p=0,28*). The average ICU stay was 2,76 days, and the average total amount of admission days in the neonatal period 10,11 days. This stay was slightly longer on average in cases with an abnormal genotype (12,67 days) and cases where an amniocentesis was not performed antenatally (12,45 days).

The rate of early neonatal death was 15,38% (4 cases) of those who had live births. Causes of neonatal death were either cardiac or respiratory failure. The rate of late neonatal death of those born alive was 7,69% (2 cases) and 9,09% of those who had survived the first week of life. Causes of late neonatal death were noted to be sepsis or respiratory failure.

Of babies born with an isolated AVSD, 15,38% demised in the neonatal period as compared to 30,77% of those who had one more associated anomaly. This difference was not statistically significant (*p=0,322*). There was also no statistically significant association between neonatal death and having an abnormal karyotype (*p=0,630*).

The average weight of those born alive was 2616g, while the average birth weight of those who sustained a neonatal death was 2201g.

Infancy

The average number of admission days in infancy was 41,47. Of the 26 born alive; 11 survived infancy and were alive at a year of life (42,31%). This amounts to 20% of the original cohort, or 29,73% of those who did not have a TOP. One of the cases that survived infancy unfortunately demised 10 days after his first birthday.

Forty-six percent (46,15% - n=12) of those born alive had corrective cardiac surgery during the first year of life. Types of surgical procedures included AVSD repairs, pulmonary artery banding, patent ductus arteriosus stenting, atrial septations or septectomies and modified BT Shunts. The maximum number of surgeries per case was 3. One case needed additional non-cardiac surgery: this was a laparotomy for malrotation. Three of the infants who had cardiac surgery demised in the neonatal period. In only one of these cases was the cause related to surgery: cardiorespiratory failure developed as the left ventricle was too small to cope with the fluid load after atrial septation. Of the 12 who had a cardiac surgical intervention, 8 were alive at one year, 1 was lost to follow up.

There were 8 deaths in infancy. The causes of death were unknown in four cases, cardiac failure in 2 cases and respiratory failure secondary to pneumonia in one case. One case was referred to palliative care after he showed no improvement after repeat cardiac surgery and another demised on the way to the hospital.

Diagnostic Accuracy

Postnatal echocardiograms (ECHO) were performed on 22 of the 26 born alive (84,62%). Those who did not have a formal postnatal ECHO all demised in the neonatal period. In those who had a postnatal ECHO, findings were consistent with an AVSD in 59,09% (13 cases). Antenatally, the type of AVSD was largely undetermined, while postnatally the Rastelli type was usually specified. Postnatal ECHO diagnoses that were inconsistent with the antenatal AVSD diagnosis are listed in figure 5.

Figure 5

	Inconsistent Post-Natal ECHO results (9 of 22)
1.	Tricuspid atresia + VSD
2.	Normal heart
3.	Hypoplastic left ventricle, VSD, double outlet right ventricle (DORV), large PDA
4.	Mitral atresia, DORV, malposition of the great vessels

5.	Common Atrium, normal valves
6.	Small ASD, DORV, double inlet right ventricle, 2 valves to right ventricle
7.	Common atrium, 2 AV valves, large PDA, left isomerism, dextrocardia
8.	VSD, TGA, PA, PDA
9.	DCMO, apical VSD

Missing Data

Maternal folders: 2 maternal folders were not found, however all ultrasound data was available on the Astraia database. One of these cases only attended GSH for an ultrasound and Fetal medicine discussion, and followed up with a private obstetrician thereafter. This case was traced and records in private obtained of a delivery of a stillborn baby. The second missing maternal folder was booked for a TOP according to ultrasound data, and miscarriage confirmation was obtained from the ward register on the day. A minority of maternal folders had missing demographic data (BMI, smoking history, teratogen exposure history).

All neonatal folders were found for those born alive. Three paediatric folders at RCCH were not found, however adequate data was obtained from the Paediatric Cardiology database which detailed all echocardiograms and surgical dates. Dates of demise were correlated with Clinicom records. Only one case was lost to follow up in infancy, and information about whether this child was alive at one year or not is unknown.

Amniocentesis results or genotype results that were missing from files were traced on the National health laboratory services (NHLS) online databases: DISA or Trakcare.

Discussion

Fetal diagnosis of AVSD has a significant bearing on fetal, neonatal and infant outcomes. There is a marked impact on survival outcomes after the diagnosis has been made.

In our study, the cohort started with a total of 55 diagnoses of fetal AVSD. The rate of termination of pregnancy was 32,72% (18 cases). The rate of miscarriage or IUFD was 20% (11 cases). Of the resultant 47,27% born alive: 4 had an ENND and 2 had a LNND. A further 8 died in infancy (14,55%).

The numbers of babies who survived up until the 1st year of life was 20% (11 cases) of the original cohort. This figure represents 29,73% of the pregnancies that did not have a termination of pregnancy and 42,31% of those born alive. One case was lost to follow up: the baby was born alive, had two surgeries in infancy, was admitted for a total of 144 days in infancy and after discharge defaulted follow up.

Survival was impacted by the presence of additional anomalies, as well as the karyotype of the fetus. Of the survivors, 36% (n=4) had a normal karyotype, and the same proportion had T21. The remaining 3 survivors did not have karyotypes performed as they did not appear syndromic postnatally.

Sixty-three percent (63,64%, n=7) of the survivors had an isolated AVSD. Of the surviving infants, only one had an associated cardiac abnormality (and this had a limited impact as it was dextrocardia). The other limited structural abnormalities amongst the survivors included skeletal dysplasia, a cystic hygroma, atrial isomerism (in heterotaxy syndrome) and duodenal atresia.

Forty-five percent (45,45%, n=5) of the surviving babies' mothers were diabetic in their pregnancy (chronic or GDM). There was no statistical impact on survival by the age of the mother or the gestational age at diagnosis.

Survival is graphically displayed below:

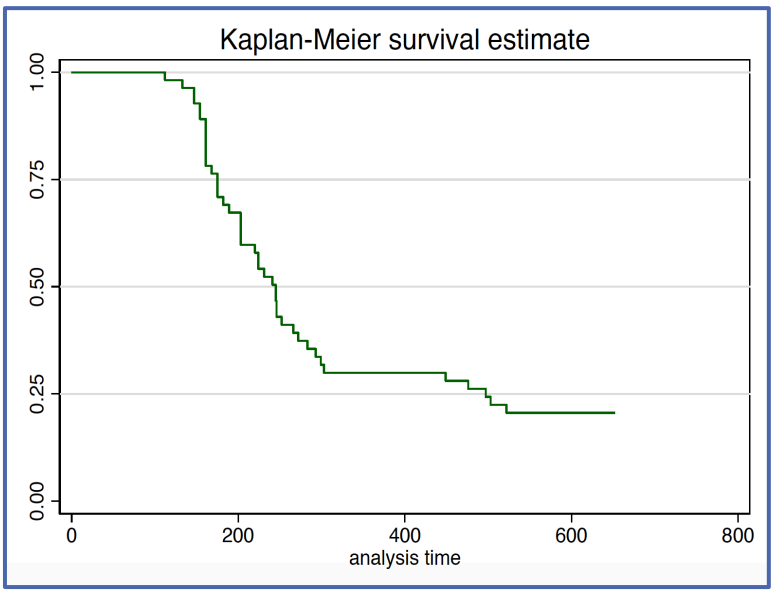


Figure 8: Graphical representation of survival from time of antenatal diagnosis until death or one year of life.

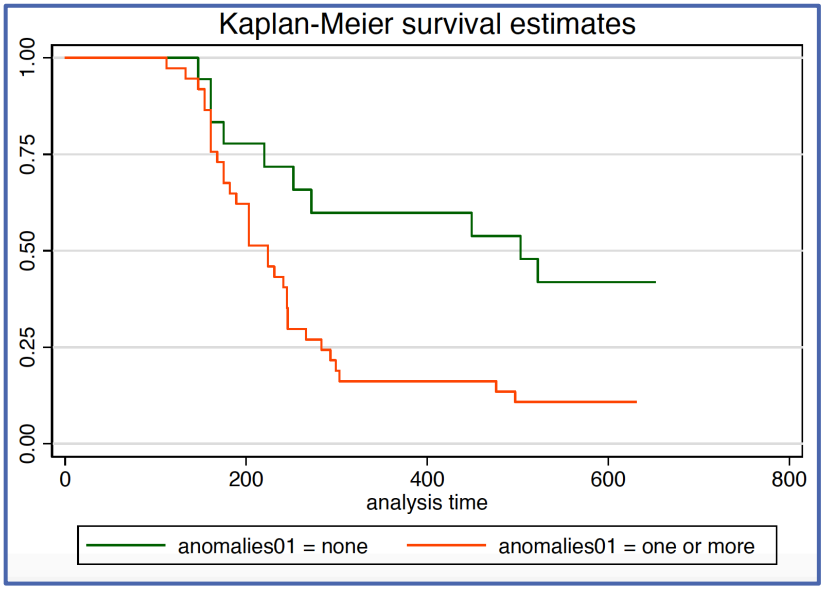


Figure 7: Graphical representation of foetal survival from antenatal diagnosis to 1 year of life with an isolated AVSD (green line) vs an AVSD with one or more additional anomaly

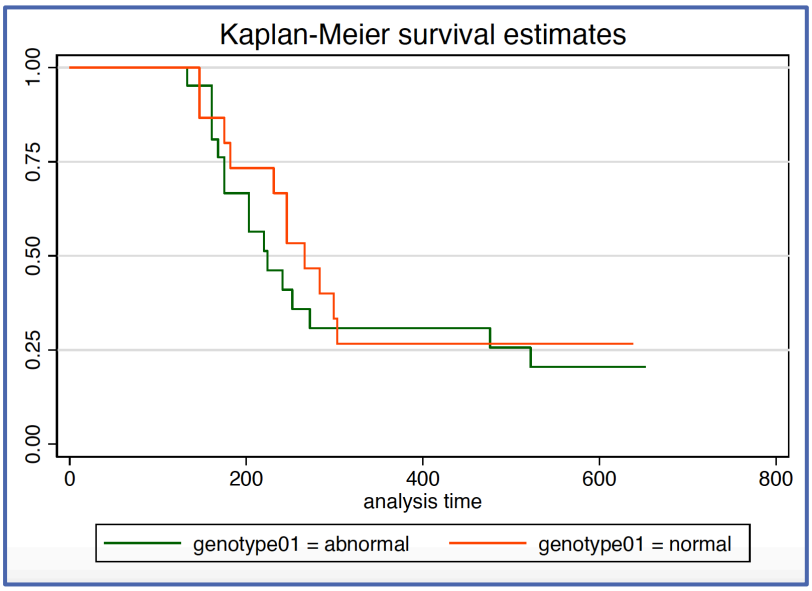


Figure 8: Graphical representation of foetal survival from antenatal diagnosis of AVSD to 1 year of life with an abnormal karyotype (green line) vs a normal karyotype.

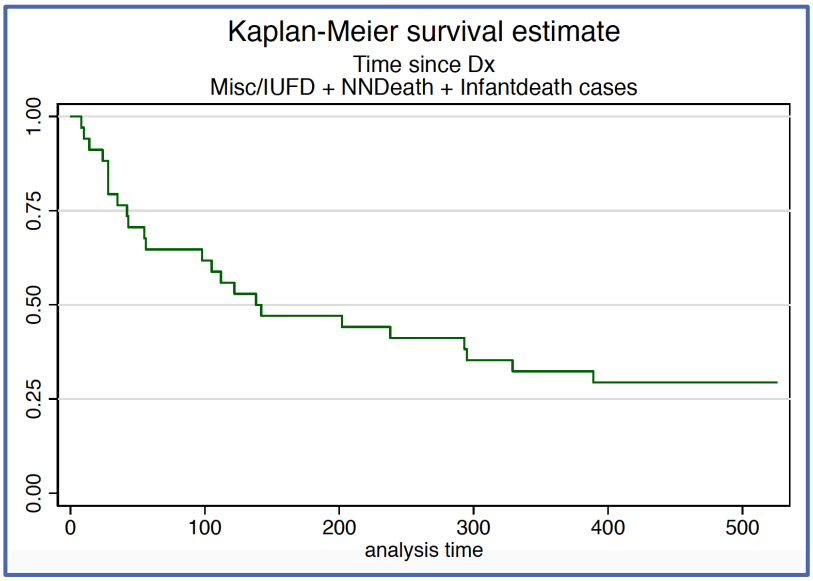


Figure 9: Graphical representation of survival excluding TOPs from antenatal diagnosis until death or one year of life.

The results of our study are in some ways similar to those from studies done previously. Figure 9 outlines similarities with previous studies.

Figure 10

Comparison of Study Findings					
	Annor et al (current study)	**Friedberg et al** [23]	**Adebo et al** [9]	**Yildirum et al** [16]	**Rasiah et al** [29]
Setting	**Cape Town, South Africa**	**California, USA**	**Minnesota, USA**	**Istanbul, Turkey**	**Birmingham, UK**
Year studied	2010-2016	2002-2004	2006-2011	2002-2007	1997-2004
Cohort Size	55	20	31	62	99
Loss to follow up/outcome unknown	2%	11%	35%	0%	4%
Average Maternal age	32	33	-	29	30
Ave GA at diagnosis	23	26	20	24	23
Agreed to prenatal genetic testing	60%	-	-	100%*	43%
Aneuploidy(%)	46%	30%	50%	40%	47%
Additional non-cardiac anomalies	55%	30%	-	60%	26%
Heterotaxy Syndrome	13%	30%	33%	19%	Not described
TOP	33%	20%	10%	58%*	35%
IUFD or miscarriage	20%	0%**	-	6,9%	15%
Neonatal Death	11%	20%**	-	8%	16%
Had surgery in infancy	22%	30%	75%***	25%	32%^

*All cases had prenatal genetic screening and all fetuses with an abnormal karyotype were terminated in the Yildirum et al study. This may reflect local policy/practice.
**No cases of miscarriage are documented in the Friedberg et al study, but multiple causes of END from prematurity were noted. Definitions of viability were not included in the study.
*** Cases in the Adebo et al study were identified in the Paediatric cardiology surgical database, and included retrospectively if they had an antenatal diagnosis.
^ It is not specified if all of these surgeries took place in infancy

Conclusions

In our cohort, the survival in fetuses diagnosed with antenatal AVSD was negatively impacted by the presence of associated structural and chromosomal abnormalities. These factors also informed patient's decision to opt for termination of pregnancy.

Results from this study will be important in counselling parents in our setting who receive an antenatal diagnosis of AVSD. Only quoting surgical repair outcomes for these patients underestimates the risk of miscarriage, spontaneous IUFD, neonatal demise and infant death unrelated to surgery that have an impact on survival.

There are various limitations to this study: this study is relatively small and so lacks power to show significant differences, if present. The study terminates at one year of life. Ongoing death in early childhood is therefore not appreciated in this study, and this may be important for parents who receive a fetal AVSD diagnosis to be aware of. Specific surgical techniques and their outcomes where not dealt with in this study.

In order to assess if prenatal AVSD diagnosis improves neonatal and infant outcomes, a further study comparing this group to the outcomes of postnatally diagnosed AVSD is necessary. There is a need for more research in this area that contextualizes the African experience of antenatal AVSD diagnosis.

In our pursuit of achieving improved maternal and child health care across Africa, antenatal ultrasound diagnosis plays an important role in identifying abnormalities, allowing informed access to termination of pregnancy for severe anomalies, and flagging fetuses that may need to be referred to higher levels of care at birth. Antenatal AVSD diagnosis is just one example. Generating data regarding the outcomes of these antenatal diagnoses is necessary for counselling of parents antenatally, planning and allocation of resources. More research on this subject needs to be done in the developing world.

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APPENDICES

APPENDIX A – DATA COLLECTION SHEETS

Maternal Data Collection Sheet

Study_ID			
Age			
BMI?			
Smoker?			
Household income	>R10 000 pm		
	R10 0000 – R30 000 pm		
	>R30 0000pm		
Date of first scan?	/ /	GAatDx	
EDD?	/ /	DateDx	/ /
Reason for tertiary ultrasound referral?			
GDM/DM?	YES ☐	NO ☐	
Previous anomaly in preg?	YES ☐	NO ☐	
Teratogen exposure?	YES ☐	NO ☐	
	Name:		
Type of AVSD	Complete AVSD		
	Partial AVSD		
	Intermediate AVSD		
	Undetermined		
Lack of offset?	YES ☐	NO ☐	
Central defect?	YES ☐	NO ☐	
Ventricular Hypoplasia?	YES ☐	NO ☐	

Unstable Crux?	YES ☐ NO ☐
AVVR?	
Associated anomalies	YES ☐ NO ☐
	If yes, Cardiac
	CNS
	GIT
	MSK
	GUT
	Heterotaxy
	Other
Amnio Offered?	YES ☐ NO ☐
Amnio Done	YES ☐ NO ☐
	Result:
TOP offered?	YES ☐ NO ☐
TOP performed?	YES ☐ NO ☐
Fetal Complication?	YES ☐ NO ☐
	If yes: IUFD? ☐
	AEDF or rEDF? ☐
	Hydrops? ☐
	Fetal Distress? ☐
	Other:
Obstetric Complication?	YES ☐ NO ☐
	If yes: APH? ☐
	Preterm labour? ☐
	GPE☐ C☐M?
	Other:

Post-mortem offered?	YES ☐ NO ☐
	Diagnosis:

Neonatal Data Collection Sheet

Study_ID		
Date of birth	/ /	
Gestational age at birth		
Birth Weight		
APGAR Score (5min/10min)	/	
Neonatal Resuscitation	YES ☐ NO ☐	
	BVM?	
	CPR?	
	Adrenaline?	
	Intubation?	
Moderate or Severe HIEearly	YES ☐ NO ☐	
EarlyHIE Score		
LaterHIE Score		
Neonatal Period:	Oxygen dependency (unable to wean)?	
	ICU Stay and days?	
	Feeding difficulties?	
	Congestive cardiac failure?	
Early Neonatal Death?	YES ☐ NO ☐	
	If yes: Infection? ☐	
	Respiratory failure? ☐	
	Cardiac Arrest? ☐	
	Other:	
	Day of Life: Date of Death:	

Late Neonatal Death	YES ☐ NO ☐
	If yes: Cardiac Failure? ☐
	Respiratory complication? ☐
	Sepsis? ☐
	Surgical complication? ☐
	Other:
	Day of Life: Date of death:
Post Natal ECHO:	YES ☐ NO ☐
Post Natal Diagnosis	Type:
	Rastelli Type:
	AVVR:
Associated abnormalities:	
Genotyping	YES ☐ NO ☐
	Result:
Duration of neonatal admission (days) :	_____ days
Inpatient transfer to RCCH	YES ☐ NO ☐
If death, post-mortem?	YES ☐ NO ☐
	Diagnosis:

Infant Data Collection Sheet

Study_ID	
Revised ECHO?	YES ☐ NO ☐
	Diagnosis?
	Rastelli:
	AVVR:
Surgery obtained	YES ☐ NO ☐
	Type:
	Date:
	Complication:
	Number of surgeries:
NonCardiac Surgery:	
Further surgery planned as at 1 year?	YES ☐ NO ☐
Any developmental delay noted?	YES ☐ NO ☐
Chronic anti failure treatment needed at 1 year?	YES ☐ NO ☐
Feeding Assistance?	YES ☐ NO ☐
	Type?
Days of admission in infancy? (from 1mo-6months)	
Defaulted follow up?	YES ☐ NO ☐
Infant Death	YES ☐ NO ☐
	Date:

	Age at death (months)
Anaesthetic related death:	YES ☐ NO ☐
	Cause:
Surgical related Death	YES ☐ N ☐
	Cause:

APPENDIX B – UCT HREC APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.arlefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 October 2017

HREC REF: 730/2017

Dr C Stewart
Division of Obstetrics & Gynaecology
H-Floor
OMB

Dear Dr Stewart

PROJECT TITLE: ANTENATAL AVSD DIAGNOSIS AT GROOTE SCHUUR HOSPITAL (Master's candidate-Dr C Annor)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC)for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr C Annor will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 730/2017

APPENDIX C: INSTRUCTIONS TO AUTHORS OF CHOSEN JOURNAL

Author Guidelines from South African Medical Journal (SAMJ) © 2014 Health & Medical Publishing Group

Available from:

http://www.samj.org.za/index.php/samj/about/submissions#Article_types

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General article format/layout
Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, **FULL** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the ONLY exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Research
GUIDELINE WORD LIMIT: 4 000 WORDS

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

STRUCTURED ABSTRACT

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

MAIN ARTICLE

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

RESULTS

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

DISCUSSION

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

CONCLUSIONS

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.
